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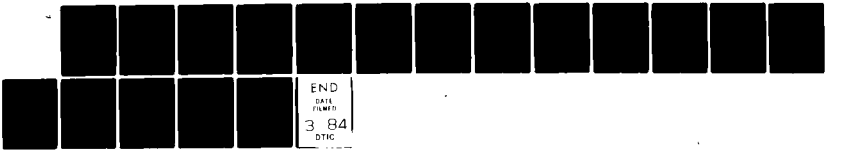

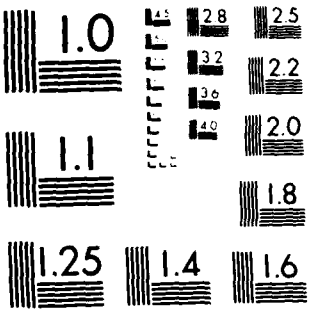

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REPORT NO. 9

BLOOD VISCOSITY CHANGES FOLLOWING SURGICAL STRESS AND TRAUMA

ANNUAL PROGRESS REPORT

By

MARTIN S. LITWIN, M.D.

JUNE, 1977

SUPPORTED BY

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

WASHINGTON, D.C. 20314

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TULANE UNIVERSITY MEDICAL SCHOOL

NEW ORLEANS, LOUISIANA 70112

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Foreword

In conducting the animal research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences - National Research Council.

ANNUAL PROGRESS REPORT

Principal Investigator: Martin S. Litwin, M.D.

Co-Principal Investigator: Stennis D. Wax, M.D.

I. TYPE OF PROPOSED STUDY

Definitive Study

II. SPECIFIC AIMS

A. To define the types of whole blood, plasma and packed cell viscosity changes occurring following surgical stress and trauma, to relate these changes to metabolic derangements associated with such states, and to define the effects of cellular aggregation and disaggregation on these variables.

B. To serve as testing laboratory for Surgical Division, U.S. Army Medical Research and Development Command, in evaluation of metabolic and blood physico-chemical effects of plasma expanders.

C. To determine the role of pulmonary microembolism associated with massive blood transfusion in development of pulmonary insufficiency.

III. HYPOTHESIS

A. Intravascular cellular aggregation occurs following physiologic insult in humans and animals. Changes leading to the initial phases of aggregation have been found to be caused by specific substances, of which thromboplastin is one, liberated from injured tissue. In the latter phases, binding to the red cell membrane of high molecular weight and high viscosity protein molecules such as fibrinogen decreases the suspension stability of

the blood and the phenomenon is perpetuated. When healing has occurred, these proteins are no longer released, suspension stability returns to normal; and aggregates are resolved.

It has been shown that experimentally-induced aggregation leads to a decrease in total body O_2 consumption, impairment of wound healing and damage to specific tissues such as the liver and kidneys. Dissolution of aggregates in animals leads to correction of these changes.

B. Amorphous aggregates of platelets, white blood cell and fibrin form in blood transfusions during storage. Administration of such blood through standard commercial blood transfusion filters permits administration of this particulate matter during blood transfusions. These aggregates cause pulmonary microembolism and lead to mechanical blockage of the small vessels of the lung. Administration of large amounts of blood containing these aggregates causes pulmonary insufficiency.

IV. ANNUAL REPORT OF PROGRESS UNDER THIS CONTRACT

Research proposed in last year's contractual agreement has been accomplished, and other related research has also been completed. Results of this work supported under the present Army Contract are reported in this Annual Progress Report.

A. Filtration Characteristics of the Polyurethane Foam (Bentley) Micropore Blood Transfusion Filter. Twenty-three units of human blood (1 unit equals approximately 500 ml of blood), stored in citrate-phosphate-dextrose solution under standard blood bank conditions at 4 C for varying periods of time, were used in

this research. Each unit of blood was filtered by gravity flow through polyurethane foam (Bentley) micropore blood transfusion filters in increments of 100 ml. Flow rates were calculated for each increment. When the flow rate became less than 20 ml/minute, the filter was judged to be occluded and a pressure of 150 mm Hg was applied using a pressure infusor. Each experiment was concluded when the filter once again became occluded. Passage through these filters resulted in decreased screen filtration pressure (SFP) of the blood and increased filter weights. Numerous microaggregates were removed and SFP returned to normal after filtration. Occlusion of the filter occurred after passage of only 2 units of whole blood.

On the basis of this research, it is concluded that the polyurethane foam (Bentley) micropore filter effectively removes microaggregates from banked blood. Because its capacity is low, it is recommended that when this filter is used, a new filter be used for each unit of blood administered. This study has recently been published (Hurley, M.J., Brown, C., Miller, E., de Jongh, D.S., and Litwin, M.S.: Polyurethane Foam (Bentley) Micropore Blood Transfusion Filter: Filtration Characteristics. Arch. Surg., 112:222-225, 1977).

B. Effects of Dextran on Microaggregate Formation in Stored Human Blood. Last year it was proposed to continue this research to better define the effects of dextran on microaggregate formation in stored whole blood (WB) and packed cells (PC). Studies reported indicated that addition of dextran 40,000 (D-40) to stored WB and PC caused a decrease in microaggregate production. During this contractual year seven different molecular weights of highly

purified dextran powders were obtained and utilized in further investigations in this area. Molecular weights ranged from 10,000 to 70,000.

Using standard blood bank techniques blood was obtained in plastic bags containing CPD from donors in the Charity Hospital of Louisiana blood bank. Each blood donation was immediately divided into two aliquots, each being 250 cc each. In order to determine which specific dextran was most effective in preventing microaggregate formation, one gram of each purified dextran derivative was added to each aliquot by passage down an integral connecting tube. After heat sealing each connecting line, one aliquot was immediately spun down, the plasma removed and the remaining cells stored as packed cells. The other was stored as whole blood. Gentle agitation of each bag insured that the powdered dextran was dissolved in the solution. Thirty-one units of blood were utilized in this research.

The purpose of this research was to determine the appropriate molecular weight dextran that would lead to optimal prevention of microaggregation in stored blood.

Last year it was reported that in a total of sixteen units of packed cells SFP of the untreated PC samples was 325 mm. When D-40 was added, SFP was reduced considerably to 195 mm. Even more striking results were observed during this experimental period; however, the addition of various molecular weights of dextran allowed better definition of the optimal molecular weight dextran for use in these experiments.

It appeared that Dextran-10 caused significantly less aggregation on the basis of SFP than did D-70. Average SFP to which intermediate dextrans were added appeared to fall between these SFP's in almost linear fashion.

Effects were most striking when D-10 was added to the CPD collection solution prior to entry of blood donation into the blood bag.

Because of the difficulties experienced in inserting purified powdered dextran into the collection apparatus, sterile saturated solutions of the various molecular weight of dextran fragments have been prepared. It is anticipated that research on this subject during the next contractual year will involve utilization of these materials.

Results of investigations during the last contractual year have been verified. It appears that dextran has little or no effect on microaggregates that have already formed in both stored PC and WB. However, microaggregate formation is considerably inhibited when dextran is added initially to the storage solution before addition of the blood donation.

Analysis of these data is continuing and this investigation will be pursued during next year.

C. Gunshot Wounds of the Abdomen. Whether or not all patients with penetrating abdominal wounds should undergo surgical exploration has been the subject of several studies. Some have stressed the conservative approach to abdominal stab wounds if no clinical signs of intraperitoneal injury are present. This sort of expectant therapy for GSWs to the abdomen has also been reported

by Ryzoff et al, (Surg., 59:650, 1966) Shaftan (J. Med. Soc. N.Y. 68:653, 1971) and Nance et al, (Ann. Surg., 179:639, 1974). Close observation of patients with abdominal stab wounds when there are no signs of intra-abdominal injury may well be justifiable, and morbidity in this condition has noticeably decreased, especially when certain diagnostic procedures such as peritoneal lavage, intravenous pyelography, and arteriography have been performed when indicated.

Others, however, favor exploration of all penetrating wounds to the abdomen, especially for GSWs. The purpose of this study was to determine whether exploration of all penetrating abdominal gunshot wounds is preferable to conservative management.

During a five-year period at Charity Hospital from July 1968 through June 1973, 277 abdominal gunshot wounds (GSWs) occurred, the overall fatality of which was 10%.

Abdominal exploration was done in all patients. No intra-abdominal injury was found in 40 patients (14%) and no death occurred in this group. There were 28 fatalities (12%) in 237 patients (86%) who had intra-abdominal injuries. Morbidity and mortality were related not only to the number of organs injured, but also to specific organs injured. The leading cause of early death was hypovolemia due to major vessel injuries. Septicemia was the most common cause of death if the patient survived the first 24 hours of hospitalization.

Penetrating abdominal stab wounds and gunshot wounds must be considered separately, and mandatory routine abdominal exploration for all penetrating gunshot wounds is advised. In stab wounds

to the abdomen, conservative management may be preferable. This study has recently been published (Dawidson, I., Miller, E. and Litwin, M.S.: Gunshot Wounds of the Abdomen: A Review of 277 Cases. Arch. Surg., 111:862-865, 1976).

D. Progression and Resolution of Changes in Pulmonary Function and Structure Due to Pulmonary Microembolism and Blood Transfusion. It was the purpose of this research to define the progression over several days of changes in pulmonary function and structure and to document the phases of recovery following transfusions to dogs of sublethal quantities of stored blood containing microaggregates. Ten dogs underwent partial exchange transfusions averaging 60% of blood volume through standard blood transfusion filters. Average screen filtration pressure (SFP) of the blood was 85 mm Hg. Pulmonary hypertension did not develop, but there were striking decreases in O_2 consumption, increases in Q_s/Q_t and decreases in Do_2. Changes became progressively more marked over the first 48 to 72 hours after the transfusions. Pulmonary function of surviving animals returned nearly to normal by the sixth day after transfusions. Pathologic examinations of the lungs of animals sequentially sacrificed over 6 days showed intravascular microemboli, alveolar cell hyperplasia and interstitial and alveolar pulmonary edema. Progressive recovery was associated with progressive resolution of all detrimental changes. In 6 animals exchange transfused 100% of their blood volumes through dacron wool (Swank) filters and in three control animals that were not transfused, there were no significant changes in pulmonary function or structure. These experiments define the progression of deterioration and recovery over 6 days of pulmonary function in dogs after sublethal

pulmonary microembolism occurring during blood transfusion. This study has recently been published (Brown, C., Dhurandhar, M.B., Barrett, J. and Litwin, M.S. with technical assistance of Miller, E. and Tennyson, J.: Progression and Resolution of Changes in Pulmonary Function and Structure Due to Pulmonary Microembolism and Blood Transfusion. Ann. Surg., 185:92-99, 1977).

E. Increased Pulmonary Arteriovenous Shunting in Humans Following Blood Transfusion. Since submission of last year's progress report, analysis of data has been completed to determine if an increase occurs in pulmonary shunting in patients receiving stored blood through standard blood transfusion filters. It was the purpose of this study to determine whether alterations in pulmonary shunting occur in humans showing transfusion of stored blood through standard transfusion filters using generally accepted transfusion techniques. If such alterations were noted, it was a further purpose of this study to compare the effects of standard blood filtration and dacron wool (Swank) microfiltration on these changes.

Twenty-three randomly selected patients who underwent major extrathoracic surgical procedures were studied. There were ten males and thirteen females, and their ages ranged between ten to sixty-eight years.

After premedication with atropine, 0.6 mg, and morphine, 8 mg, or Demeral, 50 to 75 mg, anesthesia was induced. Each patient was intubated using an oral pharyngal airway.

An intra-arterial catheter in the radial artery was used during the operation as a part of good medical management to aid

the anesthesiologist in monitoring the degree of blood oxygenation and blood pressure. Arterial blood samples for analysis were obtained from this catheter. In six patients central venous catheters were also available to obtain mixed venous blood for analysis.

When each patient had stabilized an anesthetic gas mixture of 1% halothane; 99% oxygen was administered by bag assistance. In determining pulmonary arteriovenous shunting, this gas mixture has been shown to lead to 100% oxygen saturation of hemoglobin (Marshall, B.E., et al: Pulmonary Venous Admixture Before, During and After Halothane: Oxygen Anaesthesia in Man. J. Appl. Physiol., 27:653, 1969; Michenfelder, J.D., et al: CO_2 Levels and Pulmonary Shunting in Anaesthetized Man. J. Appl. Physiol., 21:1471, 1966). The mixture was continued for at least fifteen minutes, and blood samples were obtained from the radial artery catheter and from the central venous catheter when available.

Blood samples were analyzed immediately for pH, pCO_2 and pO_2 using a Corning pH/Blood Gas Analyzer.

Percent pulmonary arteriovenous shunt (Q_s/Q_t) was calculated using the Berggren equation. Because of the high inspired O_2 tensions a fixed arteriovenous O_2 difference was assumed in those patients in whom mixed venous blood was not available for analysis. Comparison of shunt values calculated in patients in whom mixed venous blood samples were obtained to values in the same patients calculated using this assumption verified that results were comparable to within 1%.

Alveolar/arterial O_2 differences $D(A-a)O_2$ were also calculated

with the patient breathing 1% halothane: 99% oxygen.

Once the initial post-anesthetic induction Q_s/Q_t and $D(A-a)O_2$ had been determined, an appropriate nitrous oxide-oxygen gas mixture was continued throughout the operation. Five patients who underwent laparotomy also received curare for muscle relaxation.

For purposes of this tudy blood volume was assumed to be 10% of the patient's body weight. Based on this rough calculation, fourteen patients received intraoperative blood transfusions in quantities greater than 20% of their blood volumes and six patients received transfusions totalling less than 20% of their blood volumes. Three patients received no transfusions.

From every unit of blood administered, a blood sample was obtained distal to the transfusion filter, care being taken to preserve sterility and continuity of the intravenous pathway. SFP of each of these samples was determined.

All patients were divided into three groups.

Group I. Standard Transfusion Filter. Eleven patients (Table I) received blood transfusions during operation through standard blood transfusion filters.* In three of these patients transfusions were less than 20% of their calculated blood volumes (average 13%) and average postfiltration SFP of the blood was 50 mm Hg. Eight patients

* Plexitron blood solution set R 798L, Travenol Laboratories, Morton Grove, Illinois.

were transfused amounts of blood greater than 20% of their calculated blood volumes (average 34%), and average SFP of the blood was 95 mm Hg.

Group II. Dacron Wool (Swank) Transfusion Filter. Nine patients (Table I) were transfused during operation through dacron wool (Swank) transfusion filters.** In three of these patients transfusions were less than 20% of their calculated blood volumes (average 14%), and average post-filtration SFP of the blood was 5 mm Hg. Six patients were transfused amounts of blood greater than 20% of their calculated blood volumes (average 29%), and average SFP of the blood was 7 mm Hg.

Group III. Controls - No Transfusion. Three patients (Table I) did not receive blood transfusions during their operations and served as controls.

At the conclusion of the operation the anesthetic gas mixture was changed back to 1% halothane: 99% oxygen for at least 15 minutes. Using the previously described methods, post-transfusion Q_s/Q_t and $D(A-a)O_2$ were then calculated. Anesthesia was discontinued and patients allowed to recover.

All patients were followed during their postoperative courses to determine if pulmonary complications developed.

In patients transfused over 20% of blood volumes through standard filters, Q_s/Q_t and alveolar-arterial oxygen tension differences increase significantly. These changes did not occur in

** Swank transfusion filter (IL 200), Extracorporeal Medical Specialties, Inc., King of Prussia, Pennsylvania.

Table I. Averages of Variables in Patients Receiving Blood Transfusions

	Sex Female	Sex Male	Age (Years)	Weight (Lbs.)	Blood Volume (cc)	Operative Time	Est. Blood Loss (cc)	Blood Replaced (cc)	Age of Blood (Days)	SFP of Blood (mm Hg)
Group I. (Standard Filter)	6	5	40	135	6178	3 hr 48"	1300	1550	9.1	83
	(total 11)									
Group II. (Dacron Wool Filter	6	3	35	125	5672	4 hr 18"	1111	1335	9.6	6
	(total 9)									
Group III. (No Transfusion)	1	2	54	184	7044	2 hr 30"	367	0	-	-
	(total 3)									

patients transfused comparable amounts of blood through dacron wool (Swank) filters. They also did not occur in the three control patients who did not receive blood transfusions. A direct correlation was found between the absolute per cent change in Q_s/Q_t and the quantity of microaggregates passing the filter and present in the transfused blood. The maximal quantity of blood administered to any one patient in this series was five units (2500 cc) and the average SFP while elevated above normal was not inordinately high (Table I). Even though no patient in Group I developed pulmonary insufficiency after transfusion, it is distinctly possible that had larger quantities of blood been replaced, had SFP of the transfused blood been higher, or had the patient's physiological ability to compensate for this apparent insult been compromised by pre-existing lung disease, pulmonary changes might have become evident and pulmonary insufficiency might have ensued. Animal experiments previously accomplished under this contract would seem to confirm this impression.

This research represents an attempt to demonstrate that using standard generally accepted clinical transfusion techniques, transfusion of blood containing microaggregates may be hazardous to patients receiving such transfusions. The results reported are in agreement with previous results from animal experiments and indicate that microaggregates present in blood transfusions present to patients a hazard of greater magnitude than has previously been recognized.

On the basis of this research it is the opinion of the authors that before blood is administered to patients, it must first be

determined that microaggregates are not present or the blood must be administered through effective micropore blood transfusion filters. To do otherwise constitutes an unnecessary and unjustifiable danger to patients receiving such transfusions.